PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	12.01.2005
Applicant's or agent's file reference: SCB 816 PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP 03/12376	06.11.2003	14.11.2002

Applicant
DIPHARMA S.P.A. et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

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PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB 816 PCT	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/EP 03/12376	International filing date *(day/month/year)* 06.11.2003	Priority date *(day/month/year)* 14.11.2002
International Patent Classification (IPC) or both national classification and IPC C07C201/02		
Applicant DIPHARMA S.P.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 2 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
25.05.2004	12.01.2005
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Heibl, C Telephone No. +49 89 2399-8331

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP 03/12376

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-7 as originally filed

Claims, Numbers

1-10 received on 11.10.2004 with letter of 11.10.2004

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-10
	No:	Claims	
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-10
Industrial applicability (IA)	Yes:	Claims	1-10
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item V ----------

(The numbering of the prior art documents (D1,D2..) cited hereinafter corresponds to the order in which they are mentioned in the International Search Report.)

Novelty (Art.33(2) PCT)

The specific combination of technical features of the process as defined in claim 1 is not anticipated by the disclosure of any of the prior art documents **D1-D4** cited in the search report. The subject-matter of claim 1 (and dependent claims 2-7) may thus be considered as novel (Art. 33(2) PCT). The same applies with respect to the subject-matter of further independent claims 8 (product mixture obtainable by the process of claim 1) and 10 (process for the preparation of the nitric acid to be used). Moreover, it would appear that the 'nitric acid' as defined in claim 8 has not explicitly been described by the present prior art documents D1-D4.

Inventive step (Art. 33(3) PCT)

The use of urea and sulfamic acid together with nitric acid in the nitration of alcohols in order to eliminate nitrous acid (derivatives) as far as possible is well known in the art, e.g. D1, see the examples, D2, page 3, 1. paragraph, and D3, columns 1 and 2 wherein the related state of the art is summarized with respect to the influence of reaction parameters such as the nitric acid concentration, the nitration temperature, the detrimental formation of nitrous acid and its avoidance etc.
In particular, D3 which is considered to be particularly relevant, already emphasises the importance of a pre-treatment of the nitrating acid in order to avoid safety problems: "*Therefore it is essential to **completely eliminate** nitrous acid that is normally present with nitric acid **prior** to the addition of the alkanol and to remove nitrous acid as it is formed during the reaction before it can autocatalyze.*" (emphasis added; D3, column 2, lines 41-45). Accordingly, D3 suggest a pre-treatment, i.e. stabilizer addition, over a period of 15 min. to 1 hour. Only then the alcohol is added to the nitrating acid mixture (see column 3, line 56 to column 4, line 15).
Moreover, D1 clearly suggests the partial nitration of polyhydric alcohols in a two phase medium consisting of nitric acid alone (or a mixture of nitric acid and sulfuric acid) and a chlorinated hydrocarbon solvent. The concentration of the nitric acid should be in the range of 60-85%.

It is thus at present not apparent how the process for the preparing 'stabilised' nitric acid according to present claim 10 and its use in the nitration of alkylenediols (II) (see present claims 1-7) might be considered as inventive over the cited prior art teaching. If the prior art already suggests a pre-treatment of the nitric acid when nitrating alkanols (see D3), then it would appear that said pre-treatment suggests itself for the nitration of (more sensitive) alkane diols all the more.
Moreover, it is not apparent that the provision of nitric acid (conc. 83-85%) being substantially free from nitrous acid and nitrogen oxides as claimed *per se* in present claim 8 involves an inventive step having regard to the cited prior art (e.g. D3).

Industrial Applicability (Art. 33(4) PCT)

The subject-matter claimed meets the criteria of industrial applicability.

CLAIMS

1. A process for the preparation of a compound of formula

$$HO\text{-}A\text{-}ONO_2 \qquad (I),$$

wherein A is a C_2-C_6 alkylene chain,

comprising the nitration of a compound of formula

$$HO\text{-}A\text{-}OH \qquad (II),$$

wherein A is as defined above,

with nitric acid having a concentration ranging from 83 to 85% and substantially free from nitrous acid and nitrogen oxides.

2. A process as claimed in claim 1, wherein the compound of formula (I) is ethanediol-mononitrate; 1,3-propanediol-mononitrate; 1,4-butanediol-mononitrate; 1,5-pentanediol-mononitrate or 1,6-hexanediol-mononitrate.

3. A process according to any one of claims 1-2, wherein the reaction is carried out in a water-immiscible chlorinated organic solvent.

4. A process as claimed in claim 3, wherein the chlorinated organic solvent is a mono-, di-, tri- or tetra-chloro C_1-C_4-alkyl hydrocarbon.

5. A process according to any one of claims 1-4, wherein the weight ratio of nitric acid to the compound of formula (II) ranges from 10 : 1 to 15 : 1.

6. A process according to any one of claims 1-4, wherein the nitration is carried out for a time ranging from 10 to 30 minutes.

7. A process according to any one of claims 1-6, wherein the compound of formula (II) is 1,4-butanediol and the weight ratio of nitric acid to butanediol ranges from 11: 1 to 14.5: 1.

8. Nitration mixture in a water-immiscible organic chlorinated solvent comprising a compound of formula (I), as obtainable by the process of claim 1.

9. Nitric acid characterized in that it has a concentration ranging from 83 to 85% and is substantially free from nitrous acid and nitrogen oxides.

10. Process for the preparation of nitric acid as defined in claim 1 or 9 comprising the dilution of fuming nitric acid with water to a concentration of about 83 - 85% and treatment with urea or sulfamic acid, in amount ranging from 0.3 to 1% w/w, for a time ranging from 80 to 130 minutes.